PTO/SB/17 (08-00)
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FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT ($) 135.00

Complete if Known	
Application Number	08/823,999
Filing Date	March 25, 1997
First Named Inventor	Campbell Rogers
Examiner Name	P. Gambel
Group Art Unit	1644
Attorney Docket No.	MIT 7501

METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 01-2507

Deposit Account Name: Arnall Golden & Gregory, LLP

☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☒ **Payment Enclosed:**

☒ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES

		Extra Claims	Fee from below	Fee Paid
Total Claims		- 20 =	X	=
Independent Claims		- 3 =	X	=
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	80	209	40	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	135.00
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR § 1.129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 135.00

SUBMITTED BY

Complete (if applicable)

Name (Print/Type)	Patrea L. Pabst	Registration No. (Attorney/Agent)	31,284	Telephone	404-873-8794
Signature				Date	March 16, 2001

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1644

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PTO/SB/21 (6-98)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/823,999
Filing Date	March 25, 1997
First Named Inventor	Campbell Rogers
Group Art Unit	1644
Examiner Name	P. Gambel
Total Number of Pages in This Submission	
Attorney Docket Number	MIT 7501

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Additional Enclosure(s) *(please identify below)*:

Request for Oral Hearing
Return Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm *or* Individual name	ARNALL GOLDEN & GREGORY, LLP Patrea L. Pabst
Signature	
Date	March 16, 2001

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: March 16, 2001

Typed or printed name	Patrea L. Pabst		
Signature		Date	March 16, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon

Serial No: 08/823,999 Art Unit: 1644

Filed: March 25, 1997 Examiner: P. Gambel

For: MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION

REQUEST FOR ORAL HEARING

Sir:

Pursuant to 37 C.F.R. § 1.194, Appellants respectfully request an oral hearing in the Appeal to the Board of Appeals from the Office Action mailed August 16, 1999 finally rejecting claims 1-6, 8, 10-12, the Advisory Actions mailed October 28, 1999 and December 29, 1999, Notice of Non-Compliance with 37 C.F.R. 1.192(c) mailed October 6, 2000, the Advisory Action January 12, 2001, and the Examiner's Answer mailed January 16, 2001, in the above-identified application.

Also enclosed is a check in the amount of $135.00, the fee for filing a Request for Oral Hearing before the Board of Patent Appeals and Interferences, by a small entity as specified in 37 C.F.R. § 1.17(g). It is believed that no other fee is required. However, should a fee be required, the Commissioner is hereby authorized to charge any additional fees to Deposit

Account No. 01-2507. To facilitate this process, a duplicate of this Request for Oral Hearing is enclosed.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: March 16, 2001

ARNALL GOLDEN & GREGORY, LLP
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(404) 873-8795 Telefax

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this REQUEST FOR ORAL HEARING and any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: March 16, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon

Serial No.: 08/823,999 Group Art Unit: 1644

Filed: March 25, 1997 Examiner: Phillip Gambel

For: *MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION*

#31
KO
5-3-01

Assistant Commissioner
of Patents
Washington, D.C. 20231

REPLY TO EXAMINER'S ANSWER

Sir:

This is a Reply to the Examiner's Answer, mailed on January 16, 2001, in response to appellant's Brief on appeal filed June 22, 2000 in the above-identified patent application. A request for an oral hearing is enclosed along with the appropriate fee.

Those sections of the appeal brief which do not necessitate a reply have been omitted from the following.

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-6, 8, 11 and 12 are non-enabled under 35 U.S.C. § 112, first paragraph;

(2) whether claims 1-6, 8, and 10-12 are disclosed under 35 U.S.C. § 102(e) by U.S. Patent No. 5,770,198 to Coller, et al.;

(3) whether claims 1-6, 8 and 10 are disclosed under 35 U.S.C. §102(b) by Simon, et al., Circulation 92(8 Suppl), 1-110 (1995); and

(4) whether claims 1-6, 8 and 10-12 are obvious under 35 U.S.C. § 103 over Ricevuit, et al., Atherosclerosis 91, 1-14 (1991) and/or Albelda, et al., FASEB J. 8:504-512 (1994), and/or U.S. Patent No. 5,770,198 to Coller,et al. or Simon, et al., Circulation (1995), in view of still unidentified but allegedly generally known art for administering pharmaceutical compositions and Neumann, et al., JACC 27, 819-824 (1996).

(8) ARGUMENTS

(ii) Rejections Under 35 U.S.C. § 112, first pararaph

Claims 1-6, 8, 11 and 12 were rejected under 35 U.S.C. §112 as non-enabled, for anything other than anti-Mac1 antibodies, on the basis that the field is unpredictable and the specification lacks "working examples providing evidence which is reasonably predictive for the breadth of compounds which specifically inhibits or reduces leukocyte-integrin-mediated adhesion."

The examiner's argument, initially, was that the literature demonstrates restenosis has proven to be difficult to prevent or treat, since so many factors are involved. He has further argued that animal models are not useful as predictors of efficacy in humans. One should note, in passing, that the claims are not limited to treatment of restenosis in humans. Therefore this argument appears to have little merit. Moreover, appellants have provided a great deal of evidence to rebut the examiner's position. This evidence has been discounted by the examiner, not by reference to any scientific or legal support, but merely by assertion. The examiner's facts

are simply not correct. He states at page 6 of the Examiner's Answer that "Pharmaceutical therapies in the absence of *in vivo* clinical are unpredictable" then refers to factors such as degradation of proteins, proteins not reaching the target area, etc. However, appellants have provided *in vivo* clinical data, in animals, which clearly demonstrates that the proteins, specifically monoclonal antibodies, do not degrade, do reach the targets, and do result in clinical efficacy.

The Examiner has also argued that the claims are overly broad. This rejection must be made solely with respect to claims 1, 4, 5, 6, 7, 9, 11, and 12. Claims 8 and 10 are both restricted to antibodies, for which the appellants have provided both *in vitro* and *in vivo* data to support the claims. Even with respect to the classes of compounds defined by the genus of claim 1, the test is not whether the diverse compounds claimed are supported by specific working examples, but whether one skilled in the art could predict efficacy of the other members of the genus based on the data that is provided. That is, would one skilled in the art know from studies that use antibodies to Mac-1 that demonstrate efficacy in treating or preventing restenosis that one could use other compounds having the same mechanism of action. The discovery here is that the integrins, and in particular, Mac-1, play a critical role in restenosis, and that specifically inhibiting or reducing leukocyte-integrin mediated adhesion or function can, without other intervention, have a significant affect on the development of restenosis. As discussed in more detail below, the prior art cited by the examiner, discloses an antibody to glycoprotein IIb/IIa, which is cross-reactive immunologically with Mac-1. This antibody, however, does not inhibit or reduce leukocyte-integrin mediated adhesion or function and therefore has no effect on

restenosis.

Those skilled in the art can readily ascertain whether or not a compound will inhibit or reduce leukocyte-integrin mediated adhesion or function. For example, a simple *in vitro* assay using isolated monocytes (a type of leukocyte) adhesion to fibrinogen, which is blocked by exposure to the anti-Mac 1 antibody, M1/70, is described in example 1 at page 22, and shown in Figure 1. As demonstrated by the abstracts later submitted by appellants (see, for example, Simon, et al., Circulation 100(18) 1742) this assay can be used with peptides and other types of molecules to demonstrate whether or not the compound is effective to inhibit or reduce leukocyte-integrin mediated adhesion or function. Those compounds which inhibit or reduce leukocyte-integrin mediated adhesion or function are then screened for specific interaction with the integrin, for example Mac-1. The antibody cited by the examiner, c7E3, is not specific for an integrin, but cross-reactive with platelet glycoprotein IIb/IIa (see, Simon, et al., Circulation 92(8), 0519 (1995).

(iii) Rejections Under 35 U.S.C. § 102

Claims 1-6, 8 and 10 were rejected under 35 U.S.C. §102(b) as disclosed by Simon, et al., Circulation 92(8 Suppl), 1-110 (1995) or U.S. Patent No. 5,770,198 to Coller, et al.

The claims are drawn to "an effective amount of a compound specifically inhibiting or reducing leukocyte adhesion or function mediated by an integrin to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

The appellants have submitted a study which clearly demonstrates that the antibody described in the prior art, c7E3, has an effect on ischemia **but does not prevent restenosis.** See

The ERASER Investigators, "Acute Platelet Inhibition with Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation 100:799-806 (1999). This antibody also does **not** specifically bind to the integrin Mac-1. Therefore the prior art fails to meet two of the limitations of the claims and the requirements for anticipation under 35 U.S.C. §102 are not met. Inherency means that the recited property must be present, even if not recognized. Here, the property has been shown not to be present, not merely unrecognized.

(iv) Rejections Under 35 U.S.C. § 103

Claims 1-6, 8 and 10-12 were rejected as obvious under 35 U.S.C. § 103 over Ricevuit, et al., Atherosclerosis 91, 1-14 (1991) and/or Albelda, et al., FASEB J. 8:504-512 (1994), and/or U.S. Patent No. 5,770,198 to Coller,et al. or Simon, et al., Circulation (1995), in view of art for administering pharmaceutical compositions and Neumann, et al., JACC 27, 819-824 (1996).

The Examiner has failed to identify any prior art that teaches one skilled in the art to select a compound which specifically inhibits or reduces leukocyte-integrin mediated adhesion or function and can be administered in an effective amount to prevent restenosis. The only agent described in the art cited by the examiner is an antibody which does not specifically inhibit or reduce leukocyte-integrin mediated adhesions or function, c7E3, and which has been proven to not reduce restenosis. Absent some teaching to modify what is disclosed in the prior art select for a specific agent, one would not arrive at the claimed method. In fact, the teachings of the prior art lead one skilled in the art to believe that restenosis is so complex, that multiple variables must be affected to achieve a clinical result. This would lead one skilled in the art away from selection of a more specific material, rather than to that which appellants claim.

(9) SUMMARY

Claims 1-12 are enabled by the specification. No evidence has been provided by the examiner to support the rejection, and appellants have provided a detailed description in the application and in supporting data in the application and as subsequently published in support of the breadth of their claims.

Claims 1-12 define a method of preventing or inhibiting restenosis that is neither disclosed by, nor obvious from, the prior art cited by the examiner. Coller and Simon, et al. (Circulation) do not inherently disclose the claimed method. The other art cited by the examiner fails to make up for the deficiencies of Coller, et al. and Simon, et al.

(10) CONCLUSION

Claims 1-12 should be determined to be patentable under 35 U.S.C. §112, 102 and 103.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: March 16, 2001
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Appendix I: Claims as amended and on appeal

1. A method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin - mediated adhesion or function, wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18, wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or their ligands and which block the interaction of the integrins or their ligands with vascular cells; molecules which inhibit expression of the integrins or their ligands, and peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells or tissues, in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

2. The method of claim 1 wherein the leukocytes are monocytes or granulocytes.

3. The method of claim 1 wherein the injury arises from angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs.

4. The method of claim 1 wherein the composition is in a form selected from the group consisting of solutions, gels, foams, suspensions, polymeric carriers, and liposomes.

5. The method of claim 1 wherein the integrin is selected from the group consisting of LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18.

6. The method of claim 5 wherein the integrin is Mac-1 (CD11b/CD18).

7. The method of claim 6 wherein the ligand is selected from the group consisting of ICAM-1, fibrin(ogen), C3bi, and factor X.

8. The method of claim 1 wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with the integrins or their ligands and which block the interaction of the integrins or their ligands with vascular cells.

9. The method of claim 5 wherein the integrin is LFA-1 and the ligand is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3.

10. The method of claim 6 wherein the compound is an antibody or antibody fragment immunoreactive with Mac-1 (CD11b/CD18).

11. The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this Reply to the Examiner's Answer, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: March 16, 2001

Patrea Pabst